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On-line monitoring of 2D and 3D cell cultures: electrode configurations for impedance based sensors

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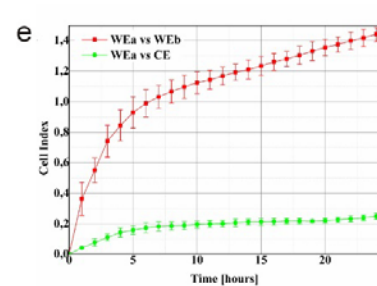
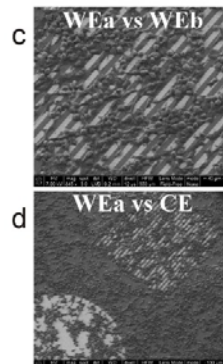
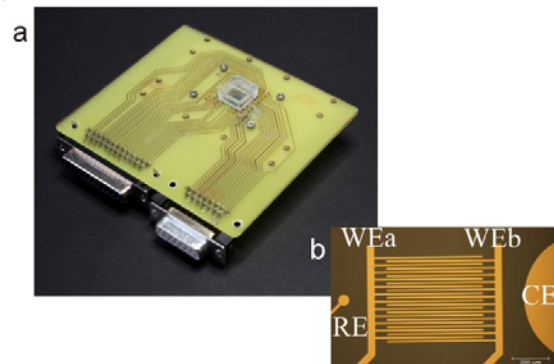
Key words: Electrical impedance spectroscopy; Interdigitated electrodes; Two-, three- and four-electrode measurements

Electrochemical impedance spectroscopy (EIS) has been proved to be a valuable technique for label-free, real-time and minimal invasive detection of cellular functions in fundamental and applied research. During the last three decades, several two-dimensional (2D) impedance-based systems have been widely used for studying cell adhesion and spreading, proliferation and death. Nowadays, there is an increasing interest towards three-dimensional (3D) cell cultures, which are proposed to create and maintain a more in vivo-like environment. EIS can be applied at different stages when developing a 2D or 3D culture setup, starting from bare scaffold and electrode characterization to monitor cell proliferation and tissue functionality.

We present theoretical and experimental comparison of several electrode configurations (or modes) both in 2D (Fig. 1A) and 3D (Fig. 1B) used for following cell growth in real-time. Two different 2D modes were explored measuring between: i) the two combs (working electrode a vs b, WEa vs WEb), interdigitated configuration (Fig. 1Aa,b,c) and ii) WE versus a large counter electrode (CE), conventional “vertical” configuration, and found that the interdigitated configuration provides a higher sensitivity when monitoring HeLa cells adhesion, spreading and growth over 24-h (Fig. 1Ad).

In 3D environment there is a need for adding the third dimension to EIS sensing for spatial resolution to gain information about distribution of cells in the scaffold (Fig. 1Ba,b,c). Moreover, electrode number, geometry and orientation need to be optimized with respect to the deriving sensitivity field distribution. In order to gain information with a good resolution, we show that several two-, three- and four-electrode measurements can be combined to create complementary sensitivity fields which individually focus on specific volumes inside the 3D cell culture and, taken together, cover the whole measurement chamber volume. This approach was tested for growing hepatoblastoma (HepG2) cells embedded within a 5% w/v gelatin scaffold (Fig. 1Bd).

A



B

